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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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FOR Comments/Response
BY
DATE 12/3/04
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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/014097	06.05.2004	06.05.2003

International Patent Classification (IPC) or both national classification and IPC
A61K47/48, A61P37/00, A61K51/04

Applicant
PURDUE RESEARCH FOUNDATION

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Dullaart, A Telephone No. +31 70 340-3290

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/014097

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☐ The following document has not been furnished:

   ☐ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-8 in part

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1-8 in part

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-8
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-8
Industrial applicability (IA)	Yes:	Claims	1-8
	No:	Claims	

2. Citations and explanations

   see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III.

In the present application, the International Searching Authority has restricted the search because of the following objections under Articles 5 and 6 PCT.
Present claims 1-8 relate to the use of an extremely large number of possible conjugates. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the conjugates claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the conjugates used in the examples.

As it is not possible to form an opinion on unsearched subject-matter, the following must be limited accordingly.

Re Item IV.

The separate inventions/groups of inventions are:

No.	Claims	Subject
1.	1-3 in part, and 5	Use of a conjugate as claimed in the manufacture of a medicament for treating lupus erythematosus, wherein the group L is a folate, and group X is an immunogen.
2.	1-3 in part, and 6-7	Use of a conjugate as claimed in the manufacture of a medicament for treating lupus erythematosus, wherein the group L is a folate, and group X is a cytotoxin.
3.	1-3 in part, and 8	Use of a conjugate as claimed in the manufacture of a medicament for treating lupus erythematosus, wherein the group L is a folate, and group X is a cytokine.
4.	1 in part, and 4	Use of a conjugate as claimed in the manufacture of a medicament for treating lupus erythematosus, wherein the group L is an antibody or an antibody fragment.

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The problem underlying the present application is to provide a new treatment of lupus erythematosus. As solution to this problem, several conjugates are proposed. The technical feature these solutions have in common is the fact, that they target te macrophages.

Compounds targeting the macrophages are already known from the prior art. Several such compounds are mentioned in **WO02/087424**. The examples demonstrate effectively how these compounds affect the macrophages. In this same document, lupus erythematosus is specifically mentioned on page 1 as one of the diseases to be treated.
This document thus anticipates the technical feature linking the different subjects contained in the present application. Therefore, this technical feature can no longer serve as special technical feature in the sense of Rule 13 PCT, linking the different subjects together.
Since there is no other technical feature, that could fulfil the role of special technical feature in the sense of Rule 13 PCT, the present application lacks unity of invention, containing the subject-matters as listed.

Since the patentability of all 4 inventions is questioned based in the same document **WO02/087424**, the present authority decided not to request an additional fee.

Re Item V.

1 The following documents are referred to in this communication:

D1: WO 02/087424 A (TURK MARY JO ; LOW PHILIP STEWART (US)) 7 November 2002 (2002-11-07)

D2: WO 99/41285 A (MEDAREX INC) 19 August 1999 (1999-08-19)

D3: WO 96/36367 A (PURDUE RESEARCH FOUNDATION) 21 November 1996 (1996-11-21)

D4: Reddy J A et al: "Folate-mediated targeting of therapeutic and imaging agents to cancers"
Critical Reviews in Therapeutic Drug Carrier Systems, vol. 15, no. 6, 1998, pages 587-627, XP000901554 ISSN: 0743-4863

D5: WO 01/74382 A (PURDUE RESEARCH FOUNDATION) 11 October 2001 (2001-10-11)

D6: Nakashima-Matsushita N et al: "Selective expression of folate receptor β and its possible role in methotrexate transport in synovial macrophages from patients with rheumatoid arthritis"
Arthritis and Rheumatism, Lippincott, Philadelphia, US, vol. 42, no. 8, August 1999 (1999-08), pages 1609-1616, XP002284073 ISSN: 0004-3591

D7: Turk M J et al: "Folate-targeted imaging of activated macrophages in rats with adjuvant-induced arthritis"
Arthritis and Rheumatism, Lippincott, Philadelphia, US, vol. 46, no. 7, July 2002 (2002-07), pages 1947-1955, XP004536129 ISSN: 0004-3591

D8: WO 98/58678 A (DEN HARTOG MARCEL THEODORUS ; BOER MARK DE (NL); PANGENETICS B V (NL)) 30 December 1998 (1998-12-30)

INVENTIONS 1-3

Document **D1** discloses the treatment of diseases mediated by macrophages. Page 1 specifically mentions SLE as disease to be treated. The procedure followed in examples 1-8 closely resembles the one followed in the present application. Also, EC20 (see present example 1) is accumulated specifically in inflamed tissue: see example 11 and figure 4.
In view of this document, which contains all the features of the present inventions, these inventions do not meet the requirements of Article 33.2 PCT for novelty.
The applicant might argue, that the present application is directed to a so-called "selection invention". In order to fulfil the criteria for a selection invention, the selection should be purposive, i.e., it should lead to a specific, different effect. The obtained effect (the problem to be solved) is, however, the same: affecting activated macrophages. Therefore, the requirements of Article 33.2 PCT for novelty are not met.

In case the applicant would consider the use of certain specific conjugates to fulfil the requirements of novelty, **D1** would be the closest prior art. The use of the specific conjugate would then be the distinguishing feature. The problem to be solved would be the treatment of lupus erythematosus.
Document **D3** discloses the conjugates of folic acid presently claimed.
Document **D4** discloses folate-mediated targeting of therapeutic agents to cancers.
Document **D5** discloses the same process of immunisation against FITC, followed by

administration of a conjugate folate-FITC. This elicits an immune response to the targeted cells. Example 1 describes the effect of folate-fluorescein isothiocyanate conjugates on survival of mice with lung tumour implants; examples 4 and 6 on tumour growth.
Document **D6** discloses the selective expression of folate receptor β and its possible role in methotrexate transport in synovial macrophages from patients with rheumatoid arthritis
Document **D7** discloses folate-targeted imaging of activated macrophages in rats with adjuvant-induced arthritis, using the compound also used in present example 1.

In principle, the skilled person would not need his inventive skills to exchange one conjugate for another. Therefore, in order to be more than merely replacing one conjugate by another, an intended effect should be demonstrated. As this has not been done in the present application, the requirements of Article 33.3 PCT for inventive step are not met.

INVENTION 4

Document **D1** discloses the treatment of diseases mediated by macrophages. Page 1 specifically mentions SLE as disease to be treated. The procedure followed in examples 1-8 closely resembles the one followed in the present application. Also, EC20 (see present example 1) is accumulated specifically in inflamed tissue: see example 11 and figure 4.
Document **D2** discloses the use of certain conjugates in affecting macrophages. The link SLE-macrophages is given on page 48, lines 3-23. Example II describes effective cell killing of macrophages using CD64 immunotoxins; example IV the detection of FcγRI-expressing cells in chronic cutaneous inflammation in humans; and example VI the effective depletion of FcγRI-expressing macrophages in vivo.
Document **D5** discloses the same process of immunisation against FITC, followed by administration of a conjugate folate-FITC. This elicits an immune response to the targeted cells. Example 1 describes the effect of folate-fluorescein isothiocyanate conjugates on survival of mice with lung tumour implants; examples 4 and 6 on tumour growth.
Document **D8** discloses an immunotoxin, in which an anti-CD40L antibody is attached to a toxin. Claims 14-16 mention SLE, and the macrophages are mentioned on page 3.

In view of each of these document, which contain all the features of the present inventions, this invention does not meet the requirements of Article 33.2 PCT for novelty.
The applicant might argue, that the present invention is a so-called "selection invention". In order to fulfil the criteria for a selection invention, the selection should be purposive, i.e., it should lead to a specific, different effect. The obtained effect (the problem to be solved) is, however, the same: treating SLE by affecting activated macrophages. Therefore, the requirements of Article 33.2 PCT for novelty are not met.

Re Item VIII.

Independent claim 1, as well as the dependent claims, encompass a genus of compounds, in which the groups L and X are defined only by their function ("a ligand capable of binding to activated macrophages" or "a vitamin-receptor binding analog or derivative thereof" for L, and "an immunogen", "a cytotoxin" or "another compound capable of altering macrophage function" for X), wherein the relationship between the structural features of the members of the genus and said function has not been defined. In the absence of such a relationship either disclosed in the as-filed application or which would have been recognised based upon information readily available to one skilled in the art, the person skilled in the art would not know how to make and use compounds that lack structural definition. The fact that one could have assayed a compound of interest using the claimed assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application) would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity. Therefore, claims 1-8 do not fulfil the requirements of Articles 5 and 6 PCT.